
Deficiencies in DNA damage repair limit the function of haematopoietic stem cells with age.

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Public Summary:

Scientific Abstract:

A diminished capacity to maintain tissue homeostasis is a central physiological characteristic of ageing. As stem cells regulate tissue homeostasis, depletion of stem cell reserves and/or diminished stem cell function have been postulated to contribute to ageing. It has further been suggested that accumulated DNA damage could be a principal mechanism underlying age-dependent stem cell decline. We have tested these hypotheses by examining haematopoietic stem cell reserves and function with age in mice deficient in several genomic maintenance pathways including nucleotide excision repair, telomere maintenance and non-homologous end-joining. Here we show that although deficiencies in these pathways did not deplete stem cell reserves with age, stem cell functional capacity was severely affected under conditions of stress, leading to loss of reconstitution and proliferative potential, diminished self-renewal, increased apoptosis and, ultimately, functional exhaustion. Moreover, we provide evidence that endogenous DNA damage accumulates with age in wild-type stem cells. These data are consistent with DNA damage accrual being a physiological mechanism of stem cell ageing that may contribute to the diminished capacity of aged tissues to return to homeostasis after exposure to acute stress or injury.

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